Diencephalic Syndrome: Clinical Features and Imaging Findings

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PURPOSE: To emphasize the importance of imaging in children with diencephalic syndrome due to hypothalamic/chiasmatic astrocytomas. **METHODS:** Findings in nine patients (mean age, 26 months) with diencephalic syndrome and hypothalamic/chiasmatic astrocytomas were analyzed retrospectively, including reviewing clinical records, imaging examinations, and follow-up studies. **RESULTS:** Symptoms and signs included failure to thrive (n = 9), nystagmus (n = 3), visual field defects (n = 1), optic pallor (n = 1), emesis (n = 2), and headache (n = 1). All patients had hypothalamic/chiasmatic masses. Five patients underwent biopsy, and, in all cases, specimens showed low-grade astrocytoma. Imaging studies were available in eight patients. All tumors were large (median maximum diameter, 3.5 cm), involved the chiasm and hypothalamus, and showed homogeneous enhancement. Three patients had hydrocephalus and two had metastases. At follow-up, five patients had recurrent disease and two had died. **CONCLUSION:** Diencephalic syndrome is a rare cause of failure to thrive in childhood, and diagnosis of a hypothalamic/chiasmatic astrocytoma might therefore be delayed. The astrocytomas associated with this syndrome are larger, occur at a younger age, and are often more aggressive than other astrocytomas arising in this region.

Index terms: Astrocytoma; Children, neoplasms; Diencephalon

Diencephalic syndrome is a rare cause of failure to thrive in infancy and early childhood. The syndrome is characterized by profound emaciation with normal caloric intake, absence of cutaneous adipose tissue, locomotor hyperactivity, euphoria, and alertness (1). It commonly occurs in association with chiasmatic and hypothalamic gliomas (1–6). It has also been described in association with other lesions, such as midline cerebellar astrocytoma, suprasellar ependymoma, suprasellar spongioblastoma, and thalamic tumor (pathologic specimens not obtained) (7–11). We retrospectively reviewed the clinical and imaging findings in a series of children with diencephalic syndrome due to hypothalamic/chiasmatic astrocytomas.

Materials and Methods

Over a 25-year period (1971 to 1996), nine patients were identified with diencephalic syndrome and hypothalamic/chiasmatic tumors at our institution (Table). Imaging studies were available in eight patients and consisted of computed tomographic (CT) scans in four patients, magnetic resonance (MR) images in three patients, and CT and MR studies in one patient. In one patient, the CT scans were not available for review. Axial 5- or 10-mm-thick CT sections were obtained before and after intravenous contrast administration in four patients. CT was done without contrast enhancement in one patient. MR examinations were performed on a 1.5-T system in four patients. Imaging parameters included 5-mm-thick sections with an intersection gap of 1 mm, a 256 × 128 matrix, and a 24-cm field of view for sagittal T1-weighted conventional spin-echo images (600/11/2 [repetition time/echo time/excitations]), fast spin-echo axial proton density–weighted images (2000/17/1), and fast spin-echo axial T2-weighted images (3200/85/1) with a 5-mm section thickness, a 2.5-mm gap, a 256 × 192 matrix, and a 24-cm field of view. Gadoteridol was administered intravenously in four patients at a dose of 0.1 mmol/kg. Axial, coronal, and

Findings in eight children with diencephalic syndrome

Case	Pathologic Findings	Recurrence, y	Surgery/Chemotherapy	Radiation Therapy, cGy	Survival	Outcome
1	None	None	None	4950	Alive, 25 y	Oligomenorrhea, infertility, precocious puberty at age 7
2*	None	None	None	4600	Alive, 17 y	Precocious puberty at age 7
3	None	7.5	None	5300	Dead, 7.5 y	Loss of visual acuity and precocious puberty at age 9
4	Low-grade astrocytoma	7	Subtotal resection	5760	Dead, 9 y	Postrecurrence blindness; progressive neurologic decline
5*	Low-grade astrocytoma	6, 7.5, 9	Biopsy, radiation; 6 y later, increase in tumor and subtotal resection; 1 y later, treated with vincristine/carboplatin; 1 y later, began oral lomustine for worsening clinical symptoms	5400	Alive, 11 y	Postrecurrence loss of visual acuity, cortisol deficiency, hypothyroidism, diabetes insipidus, precocious puberty at age 2
6*	Low-grade astrocytoma	1.5	Biopsy, then vincristine/carboplatin; after progression, subtotal resection	Stereotactic radiation therapy; 5400 after tumor growth; disseminated tumor 1.5 y later	Alive, 4 y	Loss of visual acuity, cortisol deficiency, hypothyroidism, diabetes insipidus, neuropsychiatric deficits
7*	Low-grade astrocytoma	None	Subtotal resection	Stereotactic radiation therapy, 5400	Alive, 3 y	Precocious puberty
8	Low-grade astrocytoma	0.9	Biopsy thoracic spine nodule then vincristine/carboplatin; 11 mo later, tumor growth and treated with vincristine, procarbazine, lomustine; 4 mo later, increase in tumor size then subtotal resection	None	Alive, 17 mo	Developmental delay, diabetes insipidus, right basal ganglia infarct
9	Nondiagnostic	None	Biopsy spinal nodule; palliative treatment only	None	Alive, 1 mo	Increase in size of tumor at 1 mo

* Elevated growth hormone level and paradoxical response to hypoglycemia.

sagittal T1-weighted images of the brain were subsequently obtained. In two patients, sagittal T1-weighted images of the spine were also obtained. Imaging parameters we evaluated included tumor location, size, extent, density, signal intensity, and enhancement.

In three patients, a fasting study was done for growth hormone, consisting of a 4-hour oral glucose tolerance test after administration of 1.75 g/kg oral glucose solution. Subsequently, plasma venous growth hormone levels were measured in minute increments and values obtained. In one patient, only a fasting growth hormone value could be obtained. Biopsy samples of the hypothalamic/chiasmatic tumor were available from five patients for pathologic analysis by light microscopy, including hematoxylin-eosin staining.

Results

Diencephalic syndrome and hypothalamic/optic chiasmatic tumors were identified in nine patients (five boys and four girls) (Table). The mean age at diagnosis was 26 months (range, 4 to 56 months). Clinical presentations included failure to thrive (n = 9), nystagmus (n = 3), visual field defects (n = 1), optic pallor (n = 1),

emesis (n = 2), and headache (n = 1). Seven patients had a body weight below the fifth percentile, one patient was below the 10th percentile, and one patient was below the 25th percentile. Onset of failure to thrive was defined as the age at which the patient was initially documented to have crossed weight percentiles. The mean duration of failure to thrive was 12 months (range, 2 to 29 months). The mean age at which onset of failure to thrive symptoms began was 14 months (range, 1 to 32 months). In four patients, there was a markedly elevated fasting plasma growth hormone level and a paradoxical growth hormone response to hypoglycemia. In one patient, a growth hormone level was obtained but could not be included because it was not fasting. The test was not done in three patients, and the results were not available in another. None of the patients had a family history or clinical findings of neurofibromatosis.

All tumors involved the hypothalamus and chiasm (Figs 1–3). The mean maximum diameter was 3.4 cm, and the median maximum
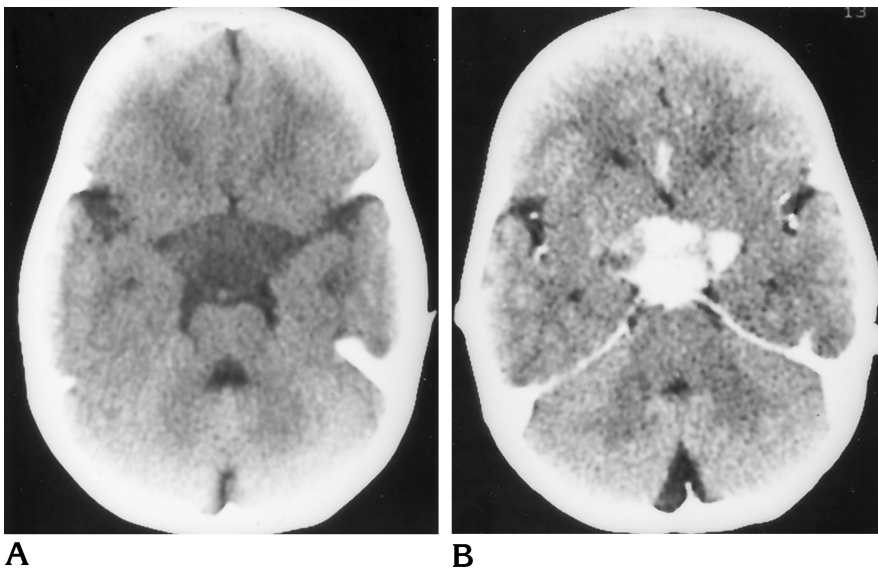
Fig 1. Case 5: 1-year-old boy with failure to thrive and nystagmus. Axial unenhanced CT scan (*A*) shows a low-attenuation suprasellar mass. After contrast administration (*B*), marked and rather uniform enhancement is seen.
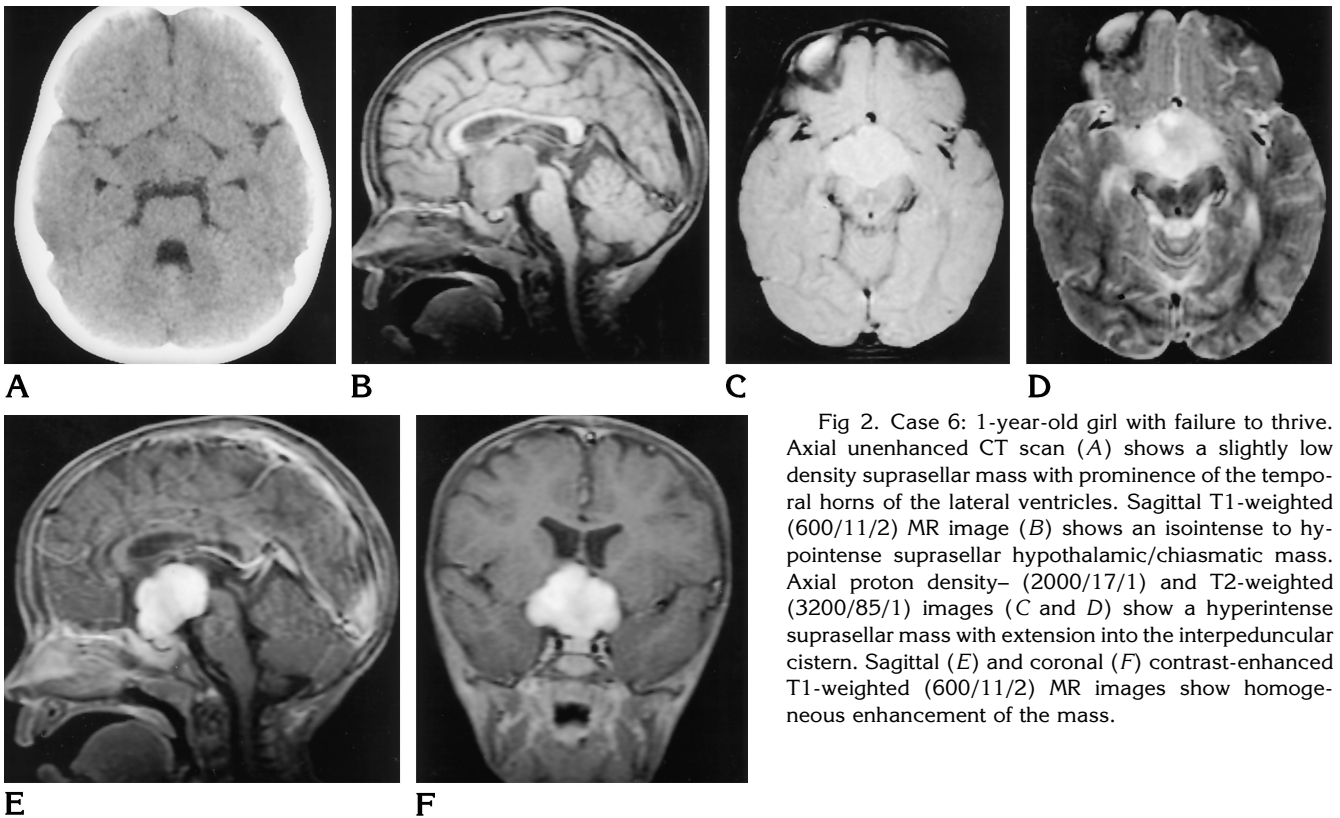

Fig 2. Case 6: 1-year-old girl with failure to thrive. Axial unenhanced CT scan (*A*) shows a slightly low density suprasellar mass with prominence of the temporal horns of the lateral ventricles. Sagittal T1-weighted (600/11/2) MR image (*B*) shows an isointense to hypointense suprasellar hypothalamic/chiasmatic mass. Axial proton density– (2000/17/1) and T2-weighted (3200/85/1) images (*C* and *D*) show a hyperintense suprasellar mass with extension into the interpeduncular cistern. Sagittal (*E*) and coronal (*F*) contrast-enhanced T1-weighted (600/11/2) MR images show homogeneous enhancement of the mass.

diameter was 3.5 cm (range, 1.3 to 5.0 cm). In six patients, there was extension superiorly into the third ventricle. In five patients, the tumors were isodense to slightly hyperdense relative to gray matter on CT scans and enhanced homogeneously in four. In the four patients examined with MR imaging, the lesions were isointense or hypointense relative to gray matter on T1-weighted images, were hyperintense on proton density– and T2-weighted images, and enhanced homogeneously in all four. Hydrocephalus occurred in five patients, mild in three and moderate in two. Two patients (cases 8 and 9) had leptomeningeal seeding of the posterior fossa and spine on initial presentation.

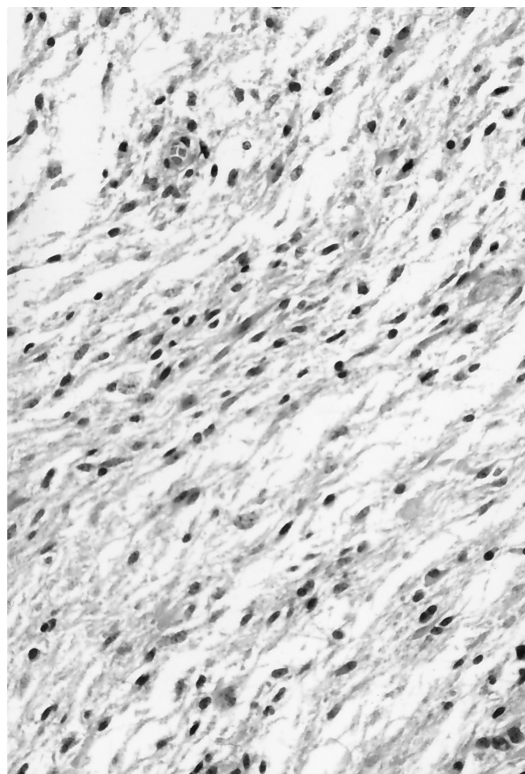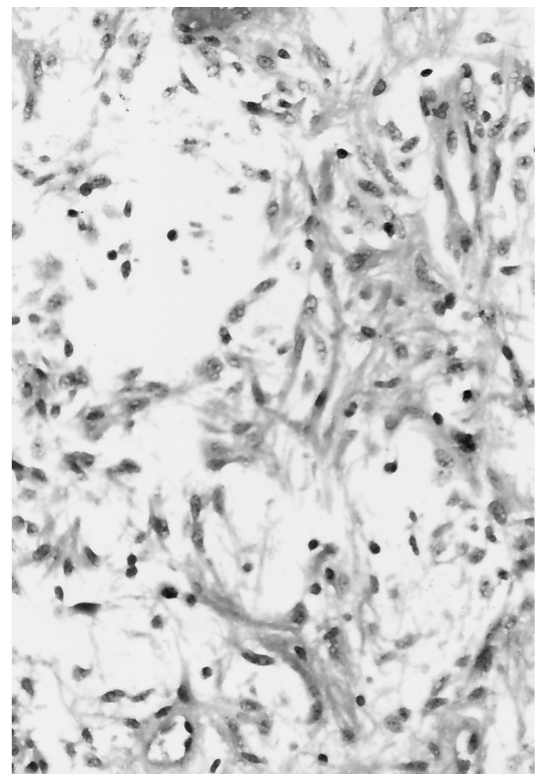Biopsy specimens of hypothalamic masses
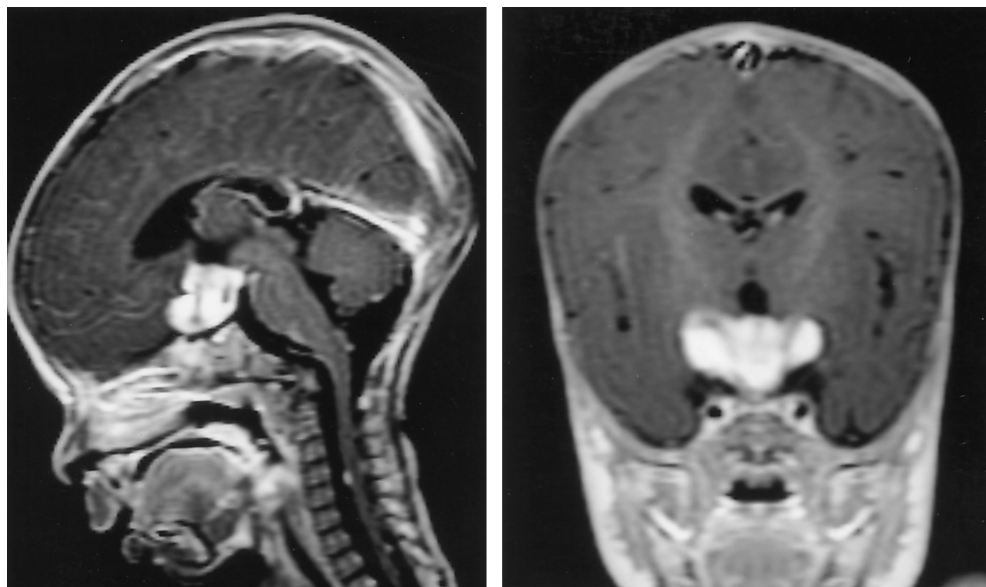
Fig 3. Case 8: 4-month-old boy with failure to thrive and weight loss.

A–C, Sagittal (*A*) and coronal (*B*) T1-weighted (600/11/2) MR images of the brain and sagittal contrast-enhanced T1-weighted (600/11/2) MR image of the spine (*C*) show a markedly enhancing hypothalamic/chiasmatic mass with leptomeningeal seeding of the cerebellum, brain stem, and spinal cord.

D and *E*, Pathologic specimens of low-grade astrocytoma (hematoxylin-eosin). In *D*, note arrangement of tumor cell processes in parallel wavy bundles. The parallel alignment of cell processes has been compared with wavy flocks of hair, and in this figure the processes stream from the lower left to the upper right. In *E*, note areas of loose organization with abundant extracellular space, and areas of more compact arrangement of tumor cells. The cells in this field show more cytoplasm, and their bipolar character is more readily visible.

were available in five patients (cases 4 through 8). In another two patients with seeding (cases 8 and 9), biopsy samples of a spinal cord nodule showed glial proliferation. Each of these tumors had similar histopathologic features. Many areas of each tumor showed a random distribution of nuclei within a fine fibrillar background. However, there were often areas in which the tumor cells were bipolar, and some areas in which the bipolar cells were arranged to form parallel alignment of processes into pilocytic bundles. Rosenthal fibers were present in three of the five biopsy samples (cases 4, 7, and 8); the other two showed areas with small round nuclei with perinuclear halos or oligodendroglialike cells (cases 5 and 7).

It was not possible to classify the tumors according to the current World Health Organization (WHO) classification, because of difficulty in distinguishing between pilocytic and fibrillary astrocytoma. In spite of bipolarity and infrequent Rosenthal fibers, a biphasic pattern, which is typical of pilocytic astrocytomas, was present in only one case (case 8, Fig 3D and E), and many areas of the tumor showed a more infiltrating pattern of individual tumor cells. There were no features of anaplasia, except in one patient who had infrequent mitoses (case 5). Vascular proliferation, high cellularity, marked nuclear pleomorphism, and necrosis were absent in all cases. Since the distinction between pilocytic astrocytoma (WHO grade 1) and well-differentiated fibrillary astrocytoma (WHO grade 2) was blurred, the tumors were typically classified as low-grade astrocytomas.

Seven patients received radiotherapy with doses ranging from 4600 to 5760 cGy, (mean, 5235 cGy) including two who underwent stereotactic radiotherapy. Three patients received radiotherapy only (cases 1–3) and two patients underwent radiation therapy after subtotal resection (cases 4 and 7). Two patients (cases 5 and 6) received a combination of radiation therapy, surgery, and chemotherapy.

Tumor recurrence was observed in a total of five patients, including one in whom dissemination developed (cases 3 through 6 and 8), during a period from 9 months to 9 years (mean, 5.6 years) after initial diagnosis and treatment. On MR images, the recurrences were similar in appearance to the original tumors. Of the nine patients in this series, two are dead (7.5 and 9 years, respectively, after therapy) and seven are alive (survival range, 1 month to 25 years;

mean, 9 years; median, 4 years). One patient (case 9) had a follow-up examination only 1 month after surgery.

Discussion

In this series of children with diencephalic syndrome, the majority (56%) were male. A similar sex predilection has been reported in other series (2, 5, 9, 10). The reason for the male predominance is not known. The mean age at presentation for our patients was 26 months. Onset in the majority of reported cases occurs in the first year of life (2, 5, 10, 12); however, the initial symptoms of failure to thrive in our series occurred at an average of 14 months of age. In a series by DeSousa et al (13), the age at diagnosis of optic nerve gliomas without diencephalic syndrome was 27 months versus 14 months in patients with diencephalic syndrome. In a series by Pierce et al (14), the median age at diagnosis of optic gliomas without diencephalic syndrome was 6.5 years (range, 1 to 21 years), which is significantly higher than the age of presentation of our patients of 26 months.

At presentation, all our patients had symptoms of failure to thrive and were emaciated. These symptoms were described originally by Russell and others (1, 2, 5, 15). The duration of the failure to thrive symptoms in our series ranged from 2 months to 29 months, with a mean of 12 months. A delay in diagnosis may occur because brain tumor is not considered early. Visual symptoms and signs (nystagmus, decreased visual fields, optic pallor) were seen in 56% of our patients, which is similar to percentages in other series, in which ocular signs were reported in an average of 66% of cases (range, 55% to 83%) (2, 5, 15). Emesis was present in only one patient (13%), a symptom that was seen in 65% (range, 52% to 74%) of cases reported previously. Locomotor overactivity, euphoria, skin pallor, hypotension, and hypoglycemia, as described in the report by Russell (1), were not seen in our patients. In our series, 44% of patients had elevated fasting plasma growth hormone levels. As reported in other series, the elevated growth hormone levels probably result from involvement of the hypothalamus. This involvement may affect the release of hypothalamic growth hormone releasing factors, and may be associated with a

paradoxical response to hypoglycemia or hyperglycemia (8, 15–18).

In the description of diencephalic syndrome by Russell (1), the diagnosis was made by surgery in four cases. Ventriculography was used in one case and showed a mass in the third ventricle. The loss of subcutaneous fat in this syndrome was noted on plain films by Poznanski and Manson (11). Later articles included descriptions of a hypothalamic mass on skull films, pneumoencephalography, air ventriculography, cerebral angiography, and radionuclide brain imaging (3–5, 9, 15, 19, 20). More recent articles (case reports) include MR and CT findings (4, 13, 17, 21, 22).

In our series, all patients had suprasellar masses involving the hypothalamus and chiasm. The differential diagnosis of a suprasellar tumor in this region in childhood includes craniopharyngioma, optic glioma, and germinoma. In this series, the tumors were not associated with cyst, calcification, hyperdensity, or hemorrhage to suggest craniopharyngioma or germinoma (23–25). On CT, the suprasellar tumors were isodense to slightly hyperdense, enhancing homogeneously. On MR imaging, the lesions were isointense to hypointense on T1-weighted images and hyperintense on proton density– and T2-weighted images, enhancing homogeneously. These findings concur with previous radiologic descriptions of optic gliomas (14, 26). It is unknown whether the imaging characteristics of optic nerve gliomas without diencephalic syndrome are different from optic nerve gliomas with the syndrome. However, the tumors in our series were larger, with a mean maximum diameter of 3.4 cm compared with the mean maximum tumor diameter in optic nerve gliomas without diencephalic syndrome of 2.8 cm (14).

The tumors most often associated with this syndrome are optic and hypothalamic astrocytomas (1–6, 15). In many cases, it is difficult to determine the exact site of tumor origin. In our series, all the tumors in which biopsy of the mass was done were low-grade astrocytomas. Astrocytoma with focal areas of oligodendrogliomalike cells has been reported previously (2, 5, 15). Only subtotal tumor resection is possible because of the involvement of visual pathways and the pituitary-hypothalamic axis (21).

Seven patients in our series (78%) are alive, with a mean follow-up of 9 years (range, 1 month to 25 years). This is slightly lower than the survival rate of approximately 90% reported by Janss et al (27) in a series of children younger than 5 years with hypothalamic/chiasmatic gliomas. A majority (56%) of the patients in our series had tumor progression, which concurs with the findings by Janss and coworkers (27) and suggests that these tumors may be more aggressive in younger children. Two of our patients had metastatic disease involving the brain and spine, despite low-grade histologic findings. Such aggressive behavior of low-grade astrocytomas in infants has also been reported previously (28, 29).

In summary, in infants with unexplained failure to thrive, the diagnosis of diencephalic syndrome should be considered. Diencephalic syndrome is most often associated with a hypothalamic/chiasmatic astrocytoma, which tends to be larger and to occur at a younger age than other astrocytomas of this region. Despite low-grade histologic findings, these tumors are often aggressive in behavior and can seed.

Acknowledgments

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